European Journal of Pharmaceutics and Biopharmaceutics 76 (2010) 253–259

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Research paper

Interaction and self-organization of human mesenchymal stem cells and neuro-blastoma SH-SY5Y cells under co-culture conditions: A novel system for modeling cancer cell micro-environment

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ARTICLE INFO

Article history:
Received 25 February 2010
Accepted in revised form 27 May 2010
Available online 2 June 2010

Keywords:
Cancer stem cell
Cell fusion
Co-culture
Mesenchymal stem cell
Micro-environment
Neuro-blastoma

ABSTRACT

The common drawback of many *in vitro* cell culture systems is the absence of appropriate micro-environment, which is formed by the combination of factors such as cell–cell contacts, extracellular matrix and paracrine regulation. Micro-environmental factors in a tumor tissue can influence physiological status of the cancer cells and their susceptibility to anticancer therapies. Interaction of cancer cells with their micro-environment and regional stem cells, therefore, is of particular interest. Development of *in vitro* systems which allow more accurate modeling of complex relations occurring in real tumor environments can increase efficiency of preclinical assays for screening anticancer drugs. The aim of this work was to study interactions between human mesenchymal stem cells (MSCs) and neuro-blastoma cancer SH-SY5Y cells under co-culture conditions on different coated surfaces to determine the effect of co-existence of cancer and stem cells on each cellular population under various stress conditions. We developed an efficient *in vitro* system for studying individual cancer and stem cell populations during co-culture using differential live fluorescent membrane labeling, and demonstrated self-organization of cancer and stem cells during co-culture on various coated surfaces. Our findings support the evidence that cancer and stem cell interactions play important roles in cellular behavior of cancer cells. These properties can be used in different fields of cancer research, tissue engineering and biotechnology.

1. Introduction

Conventional cell culture assays designed to test new therapeutics are far from representing real tissue dynamics in our body because cells in the organism are influenced by various micro-environmental factors including direct cell–cell communication, autocrine and paracrine signaling, and interactions with 3-dimensional extracellular matrix. Different *in vitro* and *in vivo* models have been employed in an effort to model such complex relations. Boyden chambers, a type of chemotaxis assay, provide cell culture with spatially but not chemically isolated environment [1]. Chambers separated by filters are proper tools for accurate determination of chemotactic behavior, as cells placed into one compartment are allowed to grow and migrate in response to concentration gradient of biologically active compounds in the other partition. Despite technical simplicity, the major drawback of such systems is lack of direct cell–cell interaction between different types of cell populations. Another popular approach for modeling natural micro-environment is the use of organo-typic cultures. In such system, a portion of live tissue is removed from the organ and cultured *in vitro*. Combination of Boyden chambers with organo-typic brain slice model was proposed to study tumor cell invasion into mammalian brain *in vitro* [2,3]. Disadvantage of such systems can be the standardization in preparation of organo-typic cultures and inability to monitor cellular behavior in real time due to 3-dimensional organization of the system. Same problems arise in spheroid culture models [4]. These obstacles were partially solved in organo-typic co-culture assays, in which myelinated axons from embryonic chicken were formed with subsequent co-culture with cancer cells [5]. Due to the 2-dimensional nature of the

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doi:10.1016/j.ejpb.2010.05.012